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EXAMINER	
HINES, JANA A	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/725,009	GEALL, ANDREW	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-9,11 and 13-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-9,11,13-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 17, 2007 has been entered.

Amendments

2. The amendments filed August 17, 2007 have been entered. Claims 1, 11 and 13 have been amended. Claims 4, 10 and 12 have been cancelled. Claims 1-3, 5-9, 11, and 13-45 are under consideration in this office action.

Withdrawal of Rejections

3. The following rejections have been withdrawn in view of applicants' amendments and arguments:

a) The rejection of claim 13 under 35 U.S.C. 112, second paragraph;

b) The rejection of claims 1-2, 5, 8-13, 15-24, 27-32, 37-39 and 40-45 under 35 U.S.C. 102(b) as being anticipated by Evans (WO 02/00844) in view of Volkin et al., (WO 97/408839);

c) The rejection of Claim 3 under 35 U.S.C. 103(a) as being unpatentable over Evans (WO 02/00844) and Volkin et al., (WO 97/408839) further in view of Balasubramaniam (US Patent 5,824,322);

d) The rejection of claims 11-14 under 35 U.S.C. 103(a) as being unpatentable over Evans (WO 02/00844) and Volkin et al., (WO 97/408839) further in view of Munsunuri et al., (WO 99/21591);

e) The rejection of claims 33-36 under 35 U.S.C. 103(a) as being unpatentable over Evans (WO 02/00844) and Volkin et al., (WO 97/408839) in view of Felgner et al., (US Patent 5,459,127).

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-3, 5-9, 11, and 13-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1 is drawn to a method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer; (ii) a polynucleotide; (iii) a cationic surfactant; and (iv) a compound selected from the group consisting of monosaccharides, disaccharides, oligosaccharides, sorbitol, hydrophilic polymers, proteins and mixtures thereof; at a temperature below the cloud point of said block copolymer to form a mixture; and (b) cold filtering the mixture; and (c) lyophilizing the mixture.

Neither the specification nor originally presented claims provides support for a method of preparing a lyophilized composition or a composition comprising a compound selected from the group consisting of mixtures thereof. Applicant did not point to support in the specification for a method of preparing a lyophilized composition or a composition comprising a compound selected from the group consisting of mixtures thereof. Moreover, applicant failed to specifically point to the identity or provide structural characteristics of the compound selected from the group consisting of mixtures thereof. Therefore, it appears that there is no support in the specification. Therefore, applicants must specifically point to page and line number support for the identity a method of preparing a lyophilized composition or a composition comprising a compound selected from the group consisting of mixtures thereof as recited by the amended claim. Therefore, amendment claim 1 incorporates new matter and is accordingly rejected.

Response to Arguments

5. Applicant's arguments filed August 17, 2007 have been fully considered but they are not persuasive. Applicants urge that paragraph [0008] provides support for mixtures thereof, because of the use of the phrase "any combination thereof". However, paragraph [0008] is drawn to the combination of ingredients within the lyophilized compositions, i.e., the block copolymer, the polynucleotide molecules, a cationic surfactant and an amorphous cryoprotectant or bulking agent. There is no teaching of mixtures of monosaccharides, disaccharides, oligosaccharides, sorbitol, hydrophilic polymers, and proteins. Even Paragraph [0011] which is drawn to suitable cryoprotectants and crystalline bulking agents, and recites examples of sugars. But the specification does not recite a compound selected from mixtures thereof. Therefore there appears to be not support for a compound selected from the group consisting of mixtures thereof, contrary to applicants' assertions.

Applicants' assert that paragraphs [0082] and [0086] provide lists of amorphous cryoprotectants and crystalline bulking agents, yet is no recitation of mixtures thereof. While there is support for single compound selection, wherein the compounds are selected from the group consisting of monosaccharides, disaccharides, oligosaccharides, sorbitol, hydrophilic polymers, and proteins, however there is no disclosure of mixtures thereof. Paragraphs [0082] and [0086] fail to recite a mixture of those compounds, contrary to applicants' assertions. Thus, the specification fails to disclose a mixture of compounds. Therefore, the rejection is maintained for reasons already of record and applicants must specifically point to page and line number support

for the identity a method of preparing a lyophilized composition or a composition comprising a compound selected from the group consisting of mixtures thereof as recited by the claim. Therefore applicants' arguments are not persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-2, 5-9, 11,13, 15-32, 37-39 and 40-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Evans (WO 02/00844) and Volkin et al., (WO 97/408839) further in view of Hunter et al., (US Patent 5,811,088).

Claim 1 is drawn to a method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer; (ii) a polynucleotide; (iii) a cationic surfactant; and (iv) a monosaccharide, disaccharide or oligosaccharide compound; at a temperature below the cloud point of said block copolymer to form a mixture; and (b) lyophilizing the mixture; and (c) lyophilizing the mixture. Claim 2 is drawn to the general formula and specific types of the block copolymer, the cationic surfactant. Claim 5 is drawn to the mixing step being performed at a temperature of about -2-8°C; Claims 6-7 are drawn to a method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and

polyoxypropylene (POP) block copolymer; and the other recited components wherein the method further comprises a cold filtration step at a temperature of about –2 to 8°C using a filter. Claim 8 is drawn to the block copolymer being CRL-1008; claim 9 is drawn to specific cationic surfactants; claim 10 is to the mixture comprising an amorphous cryoprotectant. Claim 11 is drawn the amorphous cryoprotectant being sucrose; claim 12 is drawn to the inclusion of a crystalline bulking agent; claim 13 is dawn to mixture having 1% to 20% of a crystalline bulking agent; claim 15 is drawn to the mixture comprising a pH stabilizing buffer; claims 16-19 are drawn to the physiologic buffer and concentration amounts. Claim 20 is drawn to the concentration of the cationic surfactant; claim 21 is drawn to the concentration of the block copolymer; claim 22 is drawn to the concentration of the polynucleotides; claims 23-24 are drawn to the product of claim 1; Claims 25-26 are drawn to a stable, monodispersed product produced by the method of claim 4. Claims 27-28 are drawn to the product of claim 15; claim 29 is drawn to the cationic surfactant being benethonium chloride. Claim 30 is drawn to the cationic surfactant being cetramide; claim 31 is drawn to the cationic surfactant being cetylpyridinium chloride; and claim 32 is drawn to the cationic surfactant being cetyl triethyiammonium chloride. Claims 37-39 are drawn to the compound being a monosaccharide and the produced product. Claims 40-42 are drawn to the compound being a disaccharide and the produced product. Claims 43-45 are drawn to the compound being an oligosaccharide and the produced product.

Evans teach the preparation of compositions comprising a polynucleotide, nonionic block copolymers such as polyoxyethylene (POE)/polyoxypropylene (POP)

and a cationic surfactant (POP) at a temperature below the cloud point of said block copolymer to form a mixture (page 3, lines 5-8 and 31-34 and page 32, lines 23-34). Evans states that stabilized vaccines and alternative formulations, including lyophilized formulation have been taught by the incorporated WO 97/40839 reference (page 31, lines 15-18). Evans teaches the Preparation of CRL-1005 (block copolymer) formulations containing DNA and the cationic surfactant by mixing or vortexing the components at temperatures below the cloud point of the polymer, approximately 6-7°C (page 32, lines 23-34). Evans teaches mixing the components at temperatures below the cloud point and within the recited range of claim 5. Evans recites the general POE/POP formula: $HO(C_2H_4O)_a(C_3H_60)_b(C_2H_40)_a H$, wherein (b) represents a number such that the molecular weight of the hydrophobic POP portion (C_3H_60) is less than 20,000 daltons and wherein (a) represents a number such that the percentage of hydrophilic POE portion (C_2H_4O) is between approximately 1% and 40% by weight (page 4, lines 10-17). Evans discloses surface-active block copolymer represented by CRL-005 (page 13, lines 19-21).

Evan teaches polynucleotide formulations comprising a cationic surfactant along with the block copolymer (page 13, lines 22-26). Evan teaches the cationic surfactants not limited to: benzalkonium chloride (BAK), benzethonium chloride, cetramide (which contains tetradecyltrimethylammonium bromide, dedecyltrimethylammonium bromide hexadecyltrimethyl ammonium bromide, cetylpyridinium chloride and cetyl trimethylammonium chloride (page 13, lines 26-34). The composition comprises other excipients, such as glycerol (page 23, lines 10-14). Evans teaches the inclusion of

glycerol, an amorphous cryoprotectant, as defined by the specification at paragraph [0079]. The vaccines include a saline solution such as phosphate buffered saline (PBS) (page 30, lines 18-20). The physiologically acceptable buffer in Figure 3 shows the use of 10mM sodium phosphate buffer (page 13, lines 5-27). Thus Evan teaches sodium phosphate buffer within the range of about 5mM to about 25mM.

Evans teaches the concentration range of the respective polynucleotide be from about 0.5 mg/ml to about 7.5 mg/ml, the POE and POP block copolymer be at a concentration of from about 1 to about 70 mg/ml and that the cationic surfactant be at a concentration of 0.1 to 10mM (pages 21-22, lines 32-1). Therefore Evan discloses the concentrations of the cationic surfactant at about 0.1 to 5mM, the block copolymer at about 1 to about 50 mg/ml and the polynucleotide at about 1 mg/ml to about 50 mg/ml. Evans teaches the formulation was stored at –70C and then allowed to thaw to room temperature (page 33, lines 8-9). Evans teaches providing formulations that provide for long-term stability of the vaccines (page 30, lines 22-23). However Evans do not teach a method of product further comprising a monosaccharide, disaccharide or oligosaccharide compound.

Volkin et al., teach lyophilized DNA formulation comprising amorphous disaccharide sugars, explicitly sucrose and lactose greatly stabilize the DNA (page 81, lines 11-13). Figure 12 shows lyophilized DNA formulations containing lactose or sucrose and PBS (page 15, lines 27-30). The formulation also comprises 4-5% mannitol (page 15, lines 25-31). Volkin et al., teach methods of preparations and compositions drawn to the compound being a monosaccharide, disaccharide or oligosaccharide and

the produced products. Volkin et al., teach the inclusion of mannitol, a crystalline bulking agent, as defined by the specification at paragraph [0081]. Thus, Volkin et al., teach a mixture having 1% to 20% of a crystalline bulking agent. Volkin et al., teach lyophilization allows for greater DNA stability and effectively stabilizes DNA vaccines (page 81, lines 7-11). Volkin et al., teach that during storage DNA vaccines undergo accelerated physiochemical changes, thus Volkin et al., teach formulations to optimize the stability of the DNA (page 9, lines 9-25). Volkin et al., also teach the lyophilization of DNA formulation enhances DNA stability, by reducing molecular motion, and formulations that provide the highest stability include buffers, glycerol and high DNA concentrations (page 11-12, lines 28-5). However neither Evans nor Volkin et al., teach a cold filtration step.

Hunter et al., teach cold filtration preparation and solubilization of copolymers in an ice-cold phosphate buffered saline (col. 18, lines 41-43). The cold solution was filter sterilized on 0.22um filters and stored at 4°C (col. 18, lines 43-45). Therefore, Hunter et al., the cold filtration step performed using a filter with a pore size of about 0.01 microns to 2 microns. Hunter et al., teach compositions comprising a surface active copolymer having the general formula $HO(C_2H_4O)_b(C_3H_60)_a(C_2H_40)_bH$, wherein (a) represents an integer such that the hydrophobe represented y (C_3H_60) has a molecular weight of about 1,200 to about 15,000 daltons and wherein (b) represents an integer such that the hydrophile portion represented by (C_2H_4O) constitutes approximately 1% and 50% by weight of the compound being prepared (col. 5, lines 1-17). Hunter et al., teach the composition comprising surfactants also (col. 8, lines 60-63).

Therefore it would have been prima facie obvious at the time of applicants' invention to apply polynucleotide formulations comprising saccharide compounds and crystalline bulking agents as taught by Volkin et al., to Evans method of preparing a lyophilized composition comprising: mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer; (ii) a polynucleotide; (iii) a cationic surfactant; at a temperature below the cloud point of said block copolymer to form a mixture; and lyophilizing the mixture in order to optimize the stability of the polynucleotide and provide stable long term polynucleotide formulations and further apply the cold filtration step as taught by Hunter et al., to method of Evans and Volkin et al., in order to provide sterile block copolymer formulations. One of ordinary skill in the art would have a reasonable expectation of success by modifying the method of preparation because both Evans and Volkin et al., teach the desirability of providing stable polynucleotide vaccines achieved by the specific formulations of Evans and Volkin et al., since Volkin et al., teach that disaccharide sugars such as sucrose and lactose greatly increase stabilization of lyophilized polynucleotide formulations. Moreover, one of ordinary skill in the art would have a reasonable expectation of success by modifying the method of preparation because both Evans and Volkin et al., teach the desirability of providing formulations containing block copolymers at a temperature at which they are soluble, i.e., below their cloud point, and Hunter et al., teach cold filtration of those same soluble block copolymers in an ice-cold phosphate buffered saline since filtration of the mixture rather then separate filtration clearly saves time and materials.

Furthermore, no more than routine skill would have been required to incorporate the method and formulations as taught by Hunter et al., in the method and formulation of Evans and Volkin et al., since Hunter et al., teach saving time and materials to sterilize the compositions after they have been mixed and rather than separately and individually treat the components. Finally it would have been prima facie obvious to combine the invention of Evans, Volkin et al., and Hunter et al., to advantageously decreased physiochemical changes of the polynucleotides formulations during their storage and produce a stable, monodispersed product produced by the cold filter method, since the prior art teaches that such techniques are well known to create sterile compositions.

Response to Arguments

7. Applicants' arguments filed August 17, 2007 have been fully considered but they are not persuasive.

Applicants' assert that Hunter does not disclose, suggest or other contemplate a method of producing a sterile cationic surfactant, block copolymer and polynucleotide formulation. In response to applicant's argument that Hunter does not teach a composition comprising a mixture as presently claimed, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.

See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In this case, the combined references teach a method of producing polynucleotide formulations comprising mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer; (ii) a polynucleotide; (iii) a cationic surfactant; at a temperature below the cloud point of said block copolymer to form a mixture; cold filtering the mixture; and lyophilizing in order to optimize the stability of the polynucleotide, provide stable long term polynucleotide formulations and provide sterile block copolymer formulations.

Applicants' argue that they have unexpectedly discovered that the mixture of DNA, BAK and copolymer can be sterile filtered below the cloud point of the solution, and that the mixture can be aliquoted into sterile vials before frozen storage and that filtration is unexpected because it was not known that a DNA and cationic surfactant mixture does not form a precipitate in this combination based on paragraph [0066]. However paragraph [0066] recites that microparticle reconstitution results in particles with a particle size and population polydispersity that remains unchanged during the freeze drying process. This statement fails to provide support for unexpectedly discovering that the mixture of DNA, BAK and copolymer can be sterile filtered below the cloud point of the solution, and that the mixture can be aliquoted into sterile vials before frozen storage and that filtration. Therefore applicants' argument is not persuasive.

It is well settled that unexpected results must be established by factual evidence. Applicants have not presented any experimental data. Due to the absence of tests

comparing appellant's claims with those of the closest prior art, it is concluded that applicants' assertions of unexpected results constitute mere argument."). See also *In re Lindner*, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972); *Ex parte George*, 21 USPQ2d 1058 (Bd. Pat. App. & Inter. 1991). Thus the arguments of counsel cannot take the place of evidence in the record. *In re Schulze*,346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. Therefore applicants' arguments are not persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 103

8. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Evans (WO 02/00844), Volkin et al., (WO 97/408839) and Hunter et al., (US Patent 5,811,088) further in view of Balasubramaniam (US Patent 5,824,322).

The claims are drawn to a method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer; and the other recited components wherein the block copolymer has the general formula recited by Claim 3.

The teachings and suggestions of Evans, Volkin et al., and Hunter et al., have been set forth above. In addition, Evans teaches the use of POE-POP-POE copolymers

such as CRL-1005 and the use of PLURONIC™ copolymers, which have the general organization POP-POE-POP (page 22, line 20). However Evans, Volkin et al., and Hunter et al., did not teach a POP-POE-POP copolymer wherein POP accounted for up to 20,000 daltons of the mass of the copolymer and POE represented between 1% and 50% of the copolymer by weight.

Balasubramaniam teaches compositions containing biologically-active copolymer comprising a reverse triblock copolymer of polyoxyethylene/polyoxypropylene having the formula: $HO(C_3H_60)_b(C_2H_4O)_a(C_3H_60)_bH$, wherein (b) represents a number such that the molecular weight of the hydrophobe POP $(C_3H_60)_b$ that is between approximately 2,000 and 10,000 daltons and (a) represents a number such that the percentage of hydrophilic POE (C_2H_4O) is between approximately 2% and 30% by weight (col. 13, lines 25-37). These compositions have many beneficial properties including but not limited to reducing enteric microorganisms in the gut of humans and animals (col. 17-18, lines 65-2), interfering with the adherence of microbiological organisms to surfaces (col. 18, lines 18-20), and preventing initiation of disease states and inhibiting transference of organisms (col. 18-19, lines 65-5). The preparations contain a saline solution such as physiologic phosphate buffered saline (PBS) or other physiologic salt solutions (col. 21, lines 17-20). Furthermore, Balasubramaniam teach formulations that are presented and stored in freeze-dried (lyophilized) conditions only requiring the addition of sterile water prior to use (col. 24, lines 60-64).

Therefore it would have been prima facie obvious at the time of applicants' invention to apply compositions containing biologically-active copolymer comprising a

reverse triblock copolymer of polyoxyethylene/polyoxypropylene as taught by Balasubramaniam to Evans and Volkin et al's method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer; (ii) a polynucleotide; (iii) a cationic surfactant; at a temperature below the cloud point of said block copolymer to form a mixture; and (b) lyophilizing the mixture in order to reducing enteric microorganisms in the gut of humans and animals. One of ordinary skill in the art would have a reasonable expectation of success by modifying the method of preparation because Evans, Volkin et al., and Balasubramaniam teach the desirability of providing preparations containing physiologic phosphate buffered saline and freeze-dried (lyophilized) formulations. Furthermore, no more than routine skill would have been required to exchange and use a functionally equivalent block copolymer in the method for preparing a lyophilized composition when Evans and Volkin et al., teach its advantageous properties. Finally it would have been prima facie obvious to combine the invention of Evans, Volkin et al., and Balasubramaniam to advantageously achieve the beneficial properties such as interfering with the adherence of microbiological organisms to surfaces, preventing initiation of disease states and inhibiting transference of organisms with compositions comprising the block copolymers.

Response to Arguments

9. Applicants' arguments filed August 17, 2007 have been fully considered but they are not persuasive.

Applicants' assert that Balasubramaniam is silent with regards to formulating the reverse tri-block copolymer with a polynucleotide and a cationic surfactant. Contrary to applicants assertions, Balasubramaniam teaches compositions comprising a reverse triblock copolymer of polyoxyethylene/polyoxypropylene having the formula: $HO(C_3H_60)_b(C_2H_4O)_a(C_3H_60)_bH$, wherein (b) represents a number such that the molecular weight of the hydrophobe POP $(C_3H_60)_b$ that is between approximately 2,000 and 10,000 daltons and (a) represents a number such that the percentage of hydrophilic POE (C_2H_4O) is between approximately 2% and 30% by weight (col. 13, lines 25-37) just as required by the claim.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been prima facie obvious at the time of applicants' invention to apply compositions containing biologically-active copolymer comprising a reverse triblock copolymer of polyoxyethylene/polyoxypropylene as taught by Balasubramaniam to Evans, Volkin et

al., and Hunter et al., method of preparing a lyophilized composition because Balasubramaniam teach the desirability of providing preparations containing physiologic phosphate buffered saline and freeze-dried (lyophilized) formulations having advantageous properties such as reducing enteric microorganisms in mammalian guts. Therefore applicants' arguments are not persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 103

10. Claims 11 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans (WO 02/00844) Volkin et al., (WO 97/408839) and Hunter et al., (US Patent 5,811,088) further in view of Munsunuri et al., (WO 99/21591).

Claim 11 is drawn the amorphous cryoprotectant being sucrose; claim 13 is dawn to mixture having 1% to 20% of a crystalline bulking agent; and claim 14 is drawn to the final concentration of sucrose being 10%.

The teachings of Evans, Volkin et al., and Hunter et al., have been set forth above and render obvious methods of mixing polynucleotides with POE-POP copolymers and cationic surfactants. However Evans, Volkin et al., and Hunter et al., do not teach mixing sucrose as the cryoprotectant at a concentration of 10%.

Munsunuri et al., teach sucrose being present in a polynucleotide admixture in a concentration of about 0 to about 9.25% w/v, or concentrations greater than 9%w/v wherein one skilled in the art of pharmaceutical preparations could readily adjust this characteristic of the complex (page 13, lines 8-12). Munsunuri et al., teach composition comprising soluble ionic complexes comprising a surfactant and a polynucleic acid

sequence (page 4, lines 1-5). Munsunuri et al., teach compositions containing aqueous buffers, like phosphate buffered saline for use in forming the complexes in concentrations at about 2 to about 50 mM (page 12, lines 19-29). Thus Munsunuri et al., teach the use of physiologic buffers in the mixture within the instantly recited ranges. Munsunuri et al., teach compositions that include sucrose, mannitol, sorbitol and trehalose (page 13, lines 4-8). Example 1 of Munsunuri et al., shows the mixing of compositions comprising the surfactant, the polynucleic acid sequences, a phosphate buffer, tonicity agents such as sucrose, mannitol, trehalose or any other non-ionic agent (page 30, lines 13-21). It is noted that the instant specification, at pages 22-23, names sucrose and sorbitol as amorphous cryoprotectants and mannitol and trehalose and crystalline bulking agents, thus Munsunuri et al., teach the instantly recited agents used within the instantly claimed ranges.

Therefore it would have been prima facie obvious at the time of applicants' invention to include concentrations of sucrose at about 10%w/v as taught by Munsunuri et al., in the method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer; (ii) a polynucleotide; (iii) a cationic surfactant; at a temperature below the cloud point of said block copolymer to form a mixture; and (b) cold filtering the mixture and (c) lyophilizing the mixture as taught by Evans, Volkin et al., and Hunter et al., in order to optimize the stability of the polynucleotide and provide stable long term polynucleotide formulations in order to adjust and achieve desirable tonicity in the compositions. One of ordinary skill in the art would have a reasonable expectation of success by modifying the method

of preparation because Evans, Volkin et al., Hunter et al., and Munsunuri et al., already teach sugars such as sucrose will greatly stabilize lyophilized polynucleotide formulations. No more than routine skill would have been required to incorporate sucrose within the polynucleotide method of preparation and compositions because Evans, Volkin et al., and Hunter et al, already teach a method of lyophilizing polynucleotides and surfactants in a composition wherein the composition include sucrose. Furthermore, the limitations drawn to the different concentrations for sucrose are viewed as merely optimizing the experimental parameters and not imparting patentability; thus no more than routine skill would have been required to change the concentration in the well known compositions and method of production as taught by Evans, Volkin et al., Hunter et al., and Munsunuri et al.

Response to Arguments

11. Applicants' arguments filed August 17, 2007 have been fully considered but they are not persuasive.

Applicants' argue that Musunuri does not rectify the deficiencies of Evans and Volkin and that Musunuri does not teach mixing a polynucleotide, a benzlammonium-containing surfactant and sucrose mixture with a co-polymer followed by cold filtering the mixture before lyophilizing the composition. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a benzlammonium-containing surfactant

mixture are not recited in the rejected claims. Furthermore, there is no requirement for claims 11 and 13-14 to teach particle sizes ranging from 50 nm to 230 nm in size. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore applicants' arguments are not persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 103

12. Claims 33-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans (WO 02/00844), Volkin et al., (WO 97/408839) and Hunter et al., (US Patent 5,811,088) further in view of Felgner et al., (US Patent 5,459,127).

Claim 33 is drawn to the cationic surfactant being (±)-N-(Benzyl)-N,N-dimethyl-2,3-bis(hexyloxy)-l-propanaminium bromide(Bn-DHxRIE); Claim 34 is drawn to the cationic surfactant being (±)-N-(2-Acetoxyethyl)-N,N-dimethyl-2,3-bis(hexyloxy)-1-propanaminium bromide (DHxRIE-OAc); Claim 35 is drawn to the cationic surfactant being (±)-N-(2-Benzoyloxyethyl)-N,N-dimethyl-2,3-bis(hexyloxy)-l-propanaminiurn bromide (DHxRIE-OBz); and Claim 36 is drawn to the cationic surfactant being (±)-N-(3-Acetoxypropyl)-N,N-dirnethyl-2,3-bis(octyloxy)-l-propanaminium chloride (Pr-DOctRIE-OAc).

The teachings of Evans, Volkin et al., and Hunter et al., have been set forth above and render obvious methods of mixing polynucleotides with POE-POP

copolymers and cationic surfactants. However none teach the specifically above recited cationic surfactants.

Felgner et al., teach examples of useful cationic lipids to include (+)-N-(Benzyl)-N,N-dimethyl-2,3-bis(hexyloxy)-l-propanaminium bromide(Bn-DHxRIE), (±)-N-(2-Acetoxyethyl)-N,N-dimethyl-2,3-bis(hexyloxy)-1-propanaminium bromide (DHxRIE-OAc), (±)-N-(2-Benzoyloxyethyl)-N,N-dimethyl-2,3-bis(hexyloxy)-l-propanaminiurn bromide (DHxRIE-OBz), (±)-N-(3-Acetoxypropyl)-N,N-dirnethyl-2,3-bis(octyloxy)-l-propanaminium chloride (Pr-DOctRIE-OAc). Felgner et al., teach these cationic lipids all have the same general structure (col. 4, lines 56-64). These cationic lipids are suitable for intracellular delivery of polynucleotides (col. 4, lines 50-55). The cationic lipids further comprise cationic groups that enhance the effectiveness of the lipids in interacting with the cell membrane (col. 8-9, lines 65-1). The lipid formulations are amenable to freeze-dry techniques (col. 15, lines 23-26).

Therefore it would have been prima facie obvious at the time of applicants' invention to include the cationic surfactants of claims 33-36 as taught by Felgner et al., in the method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer; (ii) a polynucleotide; (iii) a cationic surfactant; at a temperature below the cloud point of said block copolymer to form a mixture; and (b) lyophilizing the mixture as taught by Evans, Volkin et al., and Hunter et al., in order to effectively deliver polynucleotides formulations intracellularly. One of ordinary skill in the art would have a reasonable expectation of success by modifying the method of preparation because Evans, Volkin

et al., and Hunter et al., already teach cationic lipid surfactants incorporated with methods of preparation and compositions comprising block copolymers, polynucleotides, cationic surfactants and compounds. No more than routine skill would have been required to incorporate the cationic surfactants of claims 33-36 as taught by Felgner et al., into the methods of Evans, Volkin et al., and Hunter et al., because Felgner et al., teach that surfactants as enhancing the effectiveness of the lipids in interacting with the cell membrane. Furthermore, no more than routine skill would have been required to exchange and use a functionally equivalent block copolymer in the method for preparing a lyophilized composition when Evans, Volkin et al., Hunter et al., and Felgner et al., teach its advantageous use with lyophilized polynucleotide compositions.

Response to Arguments

13. Applicant's arguments filed have been fully considered but they are not persuasive.

In response to applicant's argument that Felgner et al., do not teach lyophilizing compositions comprising cationic surfactants, or adding sucrose or a copolymer to the mixture is not persuasive. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d

413, 208 USPQ 871 (CCPA 1981). In this case, it would have been prima facie obvious to include the cationic surfactants of Felgner et al., in the method of preparing a lyophilized composition as taught by Evans, Volkin et al., and Hunter et al., in order to effectively deliver polynucleotides formulations intracellularly. Furthermore, one skilled in the art would have a reasonable expectation of success by modifying the method of preparation because Evans, Volkin et al., and Hunter et al., already teach cationic lipid surfactants incorporated with methods of preparation and compositions comprising block copolymers, polynucleotides, cationic surfactants and compounds. Thus applicants' arguments are not persuasive.

Applicants' argue that they have unexpectedly discovered microparticle formation does not need to occur prior to sterilization and storage. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the occurrence of microparticle formation prior to sterilization and storage is not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore applicants' argument is not persuasive, therefore the rejection is maintained.

New Grounds of Claim Objections

14. Claims 25-26 are objected to because of the following informalities: Claims 25-26 are dependant upon cancelled claim 4. Appropriate correction is required.

Conclusion

15. No claims allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Shanon Foley, can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines
December 4, 2007

MARK NAVARRO
PRIMARY EXAMINER